REMARKS

This Amendment and Response is in response to the Office Action mailed on November 14, 2003 in connection with the above-identified application. Reconsideration of the above-identified application in view of the foregoing amendments and following remarks is respectfully requested.

Claims 35-37 are currently pending and under consideration. Claims 35-37 have been amended. No new matter has been added as a result of these amendments.

Rejection of claims 35-37 under 35 U.S.C. §112

In the Office Action, the Examiner rejects claims 35-40 [sic] under 35 U.S.C. §112, second paragraph as being indefinite. Claims 35-37 have been amended to address the Examiner's §112, second paragraph concerns. No new matter has been added as a result of these amendments. In view of these amendments, Applicants submit that this rejection is now moot and should be withdrawn.

Rejection of Claims 35-37 under 35 U.S.C. §103(a)

Claims 35-37 have been rejected under 35 U.S.C. §103 as being unpatentable over O'Rourke *et al.*, and/or Korth *et al.*, in view of Kurida *et al.*, and/or Manuelidis *et al.* Applicants respectfully traverse this rejection.

In the Office Action, the Examiner specifically argues the following:

"Kuroda et al. teach that both B cells and T cells can transmit TSE, and Manuelidis *et al.* teach that it is important to focus on these cellular populations to increase the sensitivity of assays for TSE infectivity. Both O'Rourke *et al.* and Korth *et al.* teach methods of detecting the disease form of prion protein after proteinase K digestion followed by SDS-page electrophoresis and blotting onto a membrane. One of ordinary skill in the art would have a high expectation of success in applying the techniques taught by O'Rourke *et al.* or Korth *et al.* to the infected tissue disclosed by Kuroda *et al.* or Manuelidis *et al.* It would have been obvious at the time the invention was made to improve the sensitivity of the TSE tests by collecting samples containing B cells and/or T cells and testing for the presence of TSE using an antibody based system. The ordinary artisan at the time the invention was made would have been motivated to this in order to avoid having to utilize animals in order to test for infectivity in the B and/or T cell population. The ordinary artisan at the time the invention was made would have reasonably expected that concentrating a cell type known to be infected with the TSE agent would increase the sensitivity of detection assays, including antibody-based assays. In addition, it was well known in the art at the time the invention was made that once an antibody was developed, the antibody could be used with a reasonable expectation of success to detect an antigen on intact cells, as in a buffy coat of whole blood, by either mounting them on slides for immunohistochemical analysis; or by using other techniques well known in the art at the time the invention was made for intact cell analysis with

antibodies. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references."

Applicants submit that Kuroda *et al.* and/or Manuelidis *et al.* teach that the infective agent of transmissible spongiform encephalopathy **is a virus**, and that CJD may have a hematogenous way of dissemination. With respect to Kuroda *et al.*, Applicants do not agree with the Examiner's overly broad characterization that this reference teaches "both B cells and T cells can transmit TSE". First, as mentioned above, Kuroda *et al.* mistakenly believed that CJD was caused by a virus. This was later determined not to be the case as it was subsequently been determined that TSE is the result of an abnormal prion. Second, Kuroda *et al.* report the results of a study in BALB/c mice that were infected with a Japanese strain of CJD virus. Kuroda *et al.* detected the "virus" in the brain, spleen, lung, thymus, liver, kidney and blood (but not the urine) of the infected mice at various periods in time after inoculation. Of the tissues examined, the highest infectivity was found in the brain and spleen. Kuroda *et al.* proceeded to examine these spleen cells to determine what types of cells were actually infected with the virus. Initially, Kuroda *et al.* found that spleen macrophages, T cells and B cells were infected. Of these cells, the highest concentration of the virus was found in the lymphocyte fraction. Next, Kuroda *et al.* examined the infectivity of various subpopulations of lymphocytes from these "virus"-infected mice. Kuroda *et al.* found that large lymphocytes or blastoid cells in the lower-density fractions from the spleen exhibited the most infectivity. Nowhere do Kuroda *et al.* disclose or suggest that B cells or T cells transmit TSE.

With respect to O'Rourke *et al.*, and Korth *et al.*, Applicants submit that these references describe detection of PrP^{SC} in **fixed or frozen whole tissue** using monoclonal antibodies that bind to a conserved epitope on the PrP proteins. Applicants submit that each of these references, both individually and collectively fail to teach a method that involves the steps of collecting B cells and/or T cells from a test sample and then directly testing these cell types for the presence of PrP associated with transmissible spongiform encephalopathy.

Applicants believe that a key to understanding the non-obviousness of the present invention lies in recognizing the differences between the cited references and the subject matter claimed in the present invention.

The present invention is based not only on the finding that B-cells are the crucial carriers of TSE infectivity, since that because cells can "transport" prions from lymphoid organs to nervous tissue, that T-cells also represent a secondary rout of infection. As discussed in the specification (page 31, last paragraph of the present specification):

> "The skilled reader will also appreciate that the finding that the route of infection is based on the interaction between the prions and the B-cells and the T-cells, is indeed a

revolutionary achievement which could not have been reached if one would have pursued the path indicated by the background art in the field".

Applicants submit that all the available prior art discloses is the following: (1) the belief that TSE infection was transmitted by a virus (Kuroda *et al.* and/or Manuelidis *et al.*), which was subsequently proven not to be scientifically correct, and, (2) that PrPc is expressed in all lymphocytes (O'Rourke *et al.*) and in brain homogenates or slices (Korth *et al.*). All these references, both individually and collectively, simply fail to disclose or suggest, identifying a specific type of lymphocyte as the site of replication of the prion. Therefore, a method that involves the steps of collecting B cells and/or T cells from a test sample and directly testing these cell types for the presence of prion associated with transmissible spongiform encephalopathy, is not obvious in view of the cited references.

It is these subtle, but important differences that pave the road for a distinction between "obviousness" and "obvious to try" or "obvious to experiment". The Federal Circuit has long held that it is improper to use the "obvious to try" reasoning in a 35 U.S.C. §103 rejection. In 1986, the Federal Circuit held that the district court erred in invalidating a patent on the ground that it was "obvious to try" monoclonal antibodies of a certain infinity in a sandwich immunoassay for detecting antigens. *Hybritech Inc v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). Here, the Federal Circuit stated that the prior art references discussing the production of antibodies may constitute "invitations to try monoclonal antibodies in immunoassays" but does not show obviousness since they "do not suggest how that end might be accomplished." *Id.* A similar decision was decided by the Federal Circuit in 1986. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d. 1566, 1 USPQ2d 1081 (Fed. Cir. 1986). In *Orthokinetics*, the Federal Circuit indicated that the "would have been able to produce" reason is not the standard in a 35 U.S.C. § 103 rejection: "[T]he district court's analysis employed an inappropriate 'would have been able to produce' test. The statute, §103, requires much more, i.e., that it would have been *obvious* to produce the claimed invention at the time it was made without the benefit of hindsight."

In 1987, the Federal Circuit reiterated its distinction between this improper standard and the proper obviousness standard in *N.V. Akzo v. E.I. du Pont de Nemours & Co.*, 810 F.2d 1148, 1 USPQ2d 1704 (Fed. Cir. 1987). There, the Court upheld the district court's decision because it did not apply the "obvious to try" standard. Instead, the district court properly considered the references individually and as a whole and made findings on the level of skill and on secondary considerations. *Id.* In the next year after the *N.V. Akzo* decision, the Federal Circuit held that an "obvious to experiment" is likewise not a proper standard for obviousness: "[S]elective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure." *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

It is easy to confuse the improper standard of "obvious to try" with the proper standard of "obviousness". In *re O'Farrell,* the Federal Circuit states that although any invention that would in fact have been obvious under §103 would have been in a sense, obvious-to-try, an invention that is deemed "obvious to try" is not always "obvious". The Federal Circuit explained that the "obvious to try" standard is usually improperly applied in two situations: 1) where there is a varying of parameters without any directions, and 2) where there is an exploration of a new technology or general approach. *In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988).

In the first category, the "obvious to try" is to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, but the prior art gave either no indication of which parameters were critical or no direction as to which of the many possible choices is likely to be successful. *Id.* In the second category, the "obvious to try" is to explore a new technology or general approach that seemed to be a promising field of experimentation, but the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. *Id.*

Other cases where the Federal Circuit Court has consistently held that "obvious to try" is not to be equated with obviousness under 35 U.S.C. § 103 are *Gillette co. v. S.C. Johnson & Son, Inc.* (919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1990)),*Eclochem, Inc. v. Southern California Edison Co.* (227 F.3d 1361, 56 USPQ2d 1065 (Fed. Cir. 2000)), and*In re Roemer* (258 F.3d 1303, 59 USPQ2d 1537 (Fed. Cir. 2001)),*Novo Nordisk A/S v. Becton Dickinson & Co.* (304 F.3d 1216, 64 USPQ2d 1524 (Fed. Cir. 2002)), *In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988); *Amgen, Inc. v. Chugai Pharmaceutical Co.*, Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991, *cert. denied*, 502 U.S. 856 (1991));*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re Bell*, 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993);*In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994); *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995); *Regents of University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

As seen above, the Examiner merely combines all of the references without the proper motivation in order to make the obviousness rejection. There is no discussion or suggestion in the prior art cited by the Examiner that the key roles in prion infectivity are played primarily by B-cells and secondarily by T-cells. In fact, several of the pieces of prior art cited by the Examiner incorrectly reported that TSE was a "virus". Moreover, whether prion presence is detected by the venerable proteinase K digestion or by new conformational antibodies of doubtful success is of secondary relevance. As stated above in connection with*N.V. Akzo*, "[T]here must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure". Thereupon, in view of these arguments, Applicants respectfully request that the rejection of claims 35-37 under 35 U.S.C. §103 (a) be withdrawn.

Should the Examiner have any questions concerning the above, he is respectfully requested to contact the undersigned at the telephone number listed below.

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Respectfully submitted,
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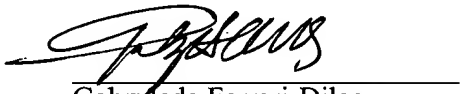

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